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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	22

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/984,900	Anthony J.F. D'Apice et al.
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

X Responsive to communication(s) filed on *Aug 18, 2000*

X This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *1-3, 46-51, 67, and 70-77* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

X Claim(s) *1-3, 46-51, 67, and 70-77* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a))

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *21*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed 8-18-00 has been entered. Claims 68 and 69 have been canceled. Claims 1, 3, 46, 51, 67 and 70-73 have been amended. Claims 74-77 have been added. Claims 1-3, 46-51, 67 and 70-77 are pending.

Since the declaration under 37 C.F.R. 1.132 filed 4-10-98 (Paper No. 7) in the present application indicating the correction of the sequencing errors of SEQ ID No. 7 was signed 7-21-97 and filed 7-30-97 (Paper No. 20) in the parent application 08/378,617, the effective filing date of the polynucleotide sequence of SEQ ID No. 7 of the present application would be the filing date of the corrected SEQ ID No. 7 sequence, i.e. 7-30-97. However, the declaration under 37 C.F.R. 1.132 filed 4-10-98 (Paper No. 7) fails to clarify the chain of possession of the original material containing the cDNA and fails to specify that the cDNA clone used for obtaining the corrected DNA sequence is the same original material as the cDNA clone for obtaining the original DNA sequence. Appropriate correction is required.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The amendment filed 8-18-00 necessitates this new ground of rejection.

The term "conservative amino acid substitution" in claim 1 is vague and renders the claim indefinite. It is unclear what kind of amino acid change constitute a conservative amino acid substitution. Is it an amino acid change that does not change the function of the protein or an amino acid change within the same group of amino acids, such as polar amino acids, positively charged amino acids. The specification of the present application fails to define the term "conservative amino acid substitution".

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claim 1 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Strahan et al., GenEmbl Accession No. L36152, 1995 (V2).

Claim 1 is directed to a nucleic acid comprising nucleotides 90-1203 of SEQ ID No. 7, a sequence encoding a polypeptide having α-1,3 galactosyltransferase activity and having the

amino acid sequence of SEQ ID No. 10, or a sequence encodes a porcine polypeptide except one or more conservative amino acid substitutions and retains a functional α-1,3 galactosyltransferase catalytic site, a functional membrane anchor domain and a functional stem region.

Strahan teaches a nucleotide sequence, GenEmbl Accession No. L36152, which is 100% identical to base 90-1203 of SEQ ID No. 7. The sequence of GenEmbl Accession No. L36152 encodes a porcine α-1,3 galactosyltransferase having the amino acid sequence which is 100% to the sequence of SEQ ID No. 10. Thus, claim 1 is clearly anticipated by Strahan.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohgi et al., 1991 (X2) in view of Strahan et al., 1995 (W2).

Claim 2 is directed to a host cell that is transformed with the nucleic acid of claim 1 as discussed above. Claim 3 is directed to a porcine α-1,3 galactosyltransferase encoded by the nucleic acid molecule of claim 1 as discussed above.

Ohgi teaches generation of a construct containing a cDNA encoding a RNase Rh protein, and the transformation of E.coli or yeast cells with said construct for the expression of the cDNA encoding a RNase Rh protein and the production of said RNase Rh protein. Ohgi does not teach the presence of the cDNA encoding a porcine α-1,3 galactosyltransferase.

Strahan teaches a cDNA sequence that encodes a pig α-1,3 galactosyltransferase having the amino acid sequence which is 100% to the sequence of SEQ ID No. 10.

It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the cDNA encoding a RNase Rh protein as taught by Ohgi with a cDNA encoding a pig α-1,3 galactosyltransferase as taught by Strahan to generate a construct containing said cDNA sequence, and transform host cells, such as E. coli or yeast cells, with said construct in order to express the cDNA in said host cells and to produce the porcine α-1,3 galactosyltransferase protein with reasonable expectation of success as taught by Ohgi.

7. Claims 46-51, 67 and 70-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sandrin et al., US Patent 5,821,117 (A) and Galili, 1993 (U2) in view of Strahan et al., 1995

(V2) and Hodges et al., 1996, US Patent No. 5,527,695 (B) and the effective filing date for the sequence of SEQ ID NO. 7 of the present application as set forth above.

Claims 46-50 are drawn to a DNA construct comprising a disrupted porcine α-1,3 galactosyltransferase (α-1,3, GT) gene, wherein the disruption is accomplished by the insertion of an exogenous sequence such as a neo^R gene or a hyg^R gene within regions such as exon 4, exon 7, exon 8, or exon 9 of the porcine α-1,3 GT gene with an amino acid sequence of SEQ ID No. 10. Claim 50 specifies the exogenous sequence is flanked at its 5' and 3' ends by FLP recombinase target site (FRT) DNA elements, and wherein stop codons have been inserted 3' to the selectable marker. Claims 51 and 74-77 are directed to a method for generating a porcine cell comprising at least one inactivated α-1,3 galactosyltransferase by introducing the DNA construct set forth above into porcine cells such that homologous recombination occurs between chromosome sequence and DNA construct. Claim 67 and 70-73 are directed to a porcine cell comprising at least one inactivated α-1,3, GT gene, wherein the disruption is by the insertion of an exogenous sequence into said gene. Claim 70 specifies the disruption is within exon 4, exon 7, exon 8, or exon 9 of the porcine α-1,3 GT gene. Claims 71 and 72 specify the exogenous sequence is a selectable marker such as neo^R gene or hyg^R gene. Claim 73 specifies the exogenous sequence is flanked at its 5' and 3' ends by FRT DNA elements.

Sandrin teaches a porcine α-1,3 galactosyltransferase cDNA sequence (SEQ ID No.2) which is 98.9% homologous (base 108-1335) to base 185-1412 of SEQ ID No.7 of the present application and discloses a λgt11 cDNA library expressing porcine α-1,3 GT in a host cell for the

isolation of the porcine α-1,3,GT cDNA (e.g. column 15-18). Sandrin discusses the hyperacute rejection response associated with xenotransplantation, particularly in the context of pig tissue as associated with antibodies reactive with galactose in an α-1,3 linkage with galactose. Sandrin teaches a method of inhibiting xenotransplant rejection in an animal patient by introducing mutants of nucleotide sequences in a vector such as plasmid, viral vector encoding α-1,3 GT, into embryonic stem cells via homologous recombination for the inactivation of wild type α-1,3 GT genes, wherein the mutant α-1,3 GT nucleotide sequences include nucleotide deletions, insertions, substitutions and additions to a wild type α-1,3 GT gene such that the resultant mutant does not encode functional galactosyl transferase. Sandrin also teaches the vectors encoding α-1,3 GT may include restriction sites for the insertion of additional genes and/or selection markers, as well as elements necessary for the propagation and maintenance of vectors within cells (e.g. column 1, 3, 9, 10).

Galili discusses that the immunological barrier by anti-Gal interacting with α-galactosyl epitopes on the discordant graft cells might be difficult to overcome by means of immunosuppression, and suggests the use of xenografts devoid of α-galactosyl epitopes obtained from nonprimate donors which are genetically engineered to lack α-1,3 GT activity by gene knockout technology or by the production of transgenic animals with anti-sense DNA to the α-1,3 GT gene (e.g. p. 482).

Sandrin et al. and Galili do not teach the polynucleotide sequence encoding the porcine α-1,3 GT with an amino acid sequence of SEQ ID No. 10 or introducing the exogenous sequence within exon 4, 7, 8, or exon 9 of the porcine α-1,3,GT gene, or using the exogenous sequence such as neo^R gene or hyg^R gene flanked at its 5' and 3' ends by FRT DNA elements.

Hodges teaches generating a DNA construct containing a FRT site and a selectable marker gene neo for a specific integration of a gene into the genome of an eukaryotic cell via homologous recombination (e.g. column 21, 22).

Strahan teaches a nucleotide sequence, GenEmbl Accession No. L36152, which is 100% identical to base 90-1203 of SEQ ID No. 7. The sequence of GenEmbl Accession No. L36152 encodes a porcine α-1,3 galactosyltransferase having the amino acid sequence which is 100% to the sequence of SEQ ID No. 10.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a selectable marker gene such as neo and a FRT site for homologous recombination as taught by Hodges for generating a DNA construct comprising a disrupted porcine α-1,3, GT gene, wherein the gene, prior to disruption, encodes the porcine α-1,3 GT with an amino acid sequence of SEQ ID No. 10 as taught by Strahan, and a porcine cell comprising said disrupted porcine α-1,3, GT gene as taught by Sandrin. It would be obvious for one of ordinary skill in the art to introduce an exogenous sequence within exon 4, 7, 8, or exon 9 of a porcine α-1,3,GT gene to interrupt α-1,3 GT gene, as Sandrin teaches, for generating mutant α-1,3 GT nucleotide sequences via nucleotide deletions, insertions, substitutions and additions to a wild type α-1,3

GT gene, such that a transgenic pig having non-functional α-1,3 GT genomic sequences would have been obtained. The tissue derived from such transgenic pig would have been useful in xenotransplantation into human patients so as to avoid hyperacute rejection response.

One having ordinary skill in the art would have been motivated to have introduced a specific disruption to a porcine α-1,3, GT gene via homologous recombination of a FRT site and to select the transformed cells containing a disrupted porcine α-1,3, GT gene with a selectable marker gene such as neo, because generation of a porcine cell comprising a disrupted porcine α-1,3, GT gene would have allowed for the development of a porcine organ lacking α-1,3 GT activity. Such would have provided the benefit of preventing xenotransplant rejection in an animal patient. Such would have been expected because it was known in the prior art that the hyperacute rejection response of xenotransplantation in a human patient would have been avoided when using a porcine organ lacking α-1,3 GT activity as taught by Sandrin and Galili.

Conclusion

No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Deborah Clark

DEBORAH J.R. CLARK
PRIMARY EXAMINER

Shin-Lin Chen, Ph.D.